Letters

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Almost 30% of anaesthetic machines in UK do not have anti-hypoxia device

Editor—In February 2001 a child died after resuscitation in an emergency department at Newham General Hospital, London, having been given 100% nitrous oxide.[1] This highlighted the ability of some anaesthetic machines to deliver a hypoxic gas mixture. Most modern machines incorporate an anti-hypoxia device in the form of a link between the oxygen and nitrous oxide controls, such that a hypoxic mixture cannot be generated. We have surveyed the prevalence of machines without an anti-hypoxia device across the United Kingdom.

In April 2001 we sent a questionnaire to 70 (23%) of the 304 college tutors of the Royal College of Anaesthetists, selected to represent all NHS regions from an official list.[2] We received replies from 54 (77%), of which 51 were suitable for analysis. The table shows our questions and the replies. Altogether, 43 respondents reported machines without an anti-hypoxia device. These were frequently located outside theatre suites, often in areas where they would be used infrequently or only in emergencies. Of the 43 respondents, 12 envisaged replacement within one year. Overall, 370 (27%) of 1357 machines had no anti-hypoxia device.

Our survey showed the existence of a large number of anaesthetic machines in NHS hospitals that, under certain conditions, could result in harm to patients. Our respondents account for about a tenth of NHS hospitals,[3] so over 3000 machines without an anti-hypoxia device may currently be used in the United Kingdom.

The European Standard for anaesthetic machines (EN740 (1998)) requires machines to have means either to prevent delivery of a gas mixture with an oxygen concentration below 20% or to give an alarm at an oxygen concentration below 20%. The previous applicable standards in the United Kingdom did not actually require anti-hypoxia devices, but by the early 1990s most new machines had one. An anaesthetic machine without an anti-hypoxia device is thus likely to be over 10 years old.

The Royal College of Anaesthetists has strongly recommended that only machines incorporating an anti-hypoxia device should be used, and has instructed that after 31 December 2002 trainees must not give nitrous oxide from machines without such a device.[4] This sets an agenda for the replacement of machines that few of our respondents envisaged meeting.

Anaesthetic machines are expensive, but this must be weighed against the personal and financial costs of a medical disaster. Implementing key lessons from adverse events in the NHS is now a central component of government policy.[5] Replacement of anaesthetic machines without anti-hypoxia devices would be in the interests of patients, managers, and clinicians alike.

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Competing interests: None declared.

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Results of postal survey about anti-hypoxia devices on anaesthetic machines in 51 NHS hospitals in UK

Question	Median (range)	Total
1 "How many anaesthetic machines are there in your hospital?" (n=51)	24 (3-74)	1357
2 "How many have flowmeters that are capable of delivering hypoxic fresh gas mix, i.e. do not have a physical hypoxic mix protection? (mere presence of monitoring, such as FiO_2 excluded)"		
Of the 51 respondents, 43 indicated a positive response to question 2:		
No of anaesthetic machines in those 43 hospitals	25 (3-74)	1172
No of those machines that did not have anti-hypoxia protection	6 (1-30)	370
If the answer to question 2 was positive, respondents were asked two further questions:		
	No(n=43)	
3 "Where are these machines?" (more than one selection per respondent allowed)		
Theatre/anaesthetic rooms	34	
Emergency department	19	
Radiology	15	
Electroconvulsive therapy	9	
Maternity	8	
Other*	8	
Coronary care unit	5	
Recovery	4	
Intensive therapy unit	3	
4 "When do you envisage replacing these machines?"		
Sooner than 12 months	12	
Longer than 12 months	7	
As soon as possible	13	
Don't know/no plans	11	

*"ITU" (3), "HDU," "lithotripsy," "spare," "dental and spare," and one not stated.

Mortality after discharge from intensive care

Only normalisation of physiology will reduce risk of mortality after discharge

Editor—The triage model described by Daly et al to identify patients at higher risk of death after discharge from intensive care seeks to address a number of important issues.[1] Daly et al used five variables (patient's age, chronic health points, length of stay in intensive care, acute physiology score, and cardiothoracic surgery) to produce a predictive model that gave a relative risk of death of 9.44 in the developmental group (mortality 14% in those at risk, 1.5% in those not at risk according to this model) and 6.76 in the validation group (mortality 28% in those at risk on day of discharge, 4% in those not at risk in the 48 hours before discharge). This adds further statistical background to previous studies, which had highlighted four of these variables as risk factors at discharge from intensive care.[2 3] The fifth variable, cardiothoracic surgery (57% of the developmental model), makes this group atypical of most intensive care units in the United

Kingdom, although this point is acknowledged in the internet version of the paper.

Daly et al claim that if patients at risk on day of discharge stay an extra 48 hours in intensive care, mortality after discharge may be reduced by 39%. This piece of statistical fast footwork is given, although no prospective component to the study shows that an extra 48 hours in intensive care will reduce the risk of (any or most or all) patients. Of the five factors in the model, only normalisation of physiology will reduce the risk of mortality after discharge (as is noted in the internet version of the paper). It may be either not possible or take much more than 48 hours to reduce the risk in an individual patient; thus the extrapolation from a predictive triage model to conclusions regarding reduction in mortality and resource requirements for 48 hours longer stay is invalid. This may be what McPherson alludes to in his accompanying editorial.[4]

No consideration of the relative timing of deaths after discharge was made. "Early" deaths, within, say, 48 hours, may reflect precipitate discharge or communication problems whereas late deaths may reflect more the standard of ward care.

None of the 20 intensive care units in this study were in hospitals with high dependency units (at that time). The advantages of such stepdown care have been long and widely recognised.[5] Further consideration is also merited of the cause of death of patients after discharge from intensive care. Although this paper excluded discharges deemed "not for resuscitation," no numbers are given. Previous studies have found 25% of deaths after intensive care were "expected" at discharge.[2]

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Research in intensive care needs to find balance between scientific method and ethics

Editor—Using an observational dataset of 13 924 patients admitted to 20 intensive care units, Daly et al have shown a surplus mortality adjusted by case mix among patients discharged to the wards, using a risk index with a cut off point for risk of death of 60%.[1] This suggests (if the model is correct) that a substantial proportion of patients must have been discharged from intensive care with a risk of death higher than this and indicates the need for prospective studies that include the circumstances surrounding death in the wards after discharge from intensive care units. We are planning such a study in the West Midlands.

McPherson says in his accompanying editorial, in which he calls for randomised studies, that provision of intensive care at the margin of possible benefit simply has to be assessed by random allocation like everything else, without providing suggestions about how this might be achieved in the context of emergency care.[2] He implies that the intensive care community is reluctant to expose its practice to scientific evaluation, using as examples the albumin controversy and arguments against randomisation on ethical grounds.

Most intensive care practitioners show enthusiasm for evaluation of their practice but have concerns about methodological issues.[3] Prospective randomised evaluation of a predictor of risk is certainly feasible between hospitals, although the potential for confounding in terms of variation in structures and processes is considerable. Random allocation of critically ill patients to different levels of care in an institution is complicated by ethical difficulties generated by the likely absence of equipoise[4] and the Hawthorne effect, as anyone familiar with acute medical care will understand. Large observational databases containing validated information from many thousands of patients provide an important alternative in this context and may well be more robust than meta-analyses in terms of the validity of their output.[5]

A research method based on collaborative networks, observational databases to adjust for case mix, and agreed standards of care should form the basis for evaluating existing technologies, incorporating prospective randomised controlled trials where this is possible. As clinical researchers, we have a duty to find a balance between rigorous scientific method and the ethical problems associated with (in this instance) persuading patients or their relatives that they should be allocated to early discharge from intensive care to understaffed and overworked hospital wards.

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Only community debate on appropriate end of life care will limit ballooning budget

Editor—McPherson's assertion that intensive care is outside the evidence based paradigm does not stand up to the evidence.[1] The management of patients in intensive care units is now more evidence based than ever before, and many decisions made by specialists in intensive care have been tested by the rigour of a randomised controlled trial.[2] Far from dismissing the Cochrane review, the intensive care community has engaged in vigorous debate on this issue. In Australia we are about to start recruitment to what will become the largest intensive care trial ever conducted—a double blind placebo controlled trial of albumin in fluid resuscitation under the auspices of the Australian and New Zealand Intensive Care Society Clinical Trials Group.

Yet it seems that it is the use of intensive care itself that McPherson considers not evidence based. Again, he is wide of the mark. We contend that, more than any other discipline, the specialists in intensive care and their specialty have been subject to trial.[3] It is true that often these studies have not been randomised, but their results are supported by the optimisation studies in surgical patients at high risk, in which randomisation has taken place.[4]

McPherson represents a traditional view in the United Kingdom that is counterproductive to change. As Daly et al show in the accompanying paper,[5] there are too few intensive care beds in the NHS. Trials to prove the effectiveness of intensive care will not influence spending since a life lost on the ward costs less than one saved in intensive care. There should be enough intensive care beds for those who need them, and available beds must be used wisely.

Nevertheless, where intensive care is recognised as highly effective—for example, in Australia—the demand for further beds may become insatiable. Unfortunately, as a profession we are getting worse at saying "no," and wise use of beds in intensive care is already passing out of the specialist's control. To put the onus of justifying expenditure for intensive care units on to intensive care specialists is unfair, as only a major general community debate about appropriate end of life care can limit the ballooning budget. We doubt that this will happen because the community, in Australia and the United Kingdom, just does not have the stomach for it.

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Dysfunctional breathing and asthma

Panic disorder needs to be considered

Editor—Thomas et al report an appreciable prevalence of dysfunctional breathing in adults with asthma and discuss the scope for wider use of breathing therapy.[1] Neither Thomas et al nor Keeley and Osman in their editorial[2] consider whether such symptoms might occur equally often in the normal population or represent panic attacks and panic disorder, well defined entities common in otherwise healthy people. Without a control group their study is incapable of identifying the prevalence of dysfunctional breathing associated specifically with asthma.

Dysfunctional breathing and the hyperventilation syndrome are by no means the same as panic syndromes, but overlap between them may be considerable. Thomas et al acknowledge limitations of the Nijmegen questionnaire.[3] This instrument cannot differentiate the "chimeric" hyperventilation syndrome from panic attacks and panic disorder. The 16 items in the Nijmegen questionnaire include "anxiety," "feeling tense," and nine of the 13 panic attack symptoms listed in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R). The questionnaire was not defined to attempt to make this distinction. A 23% lifetime prevalence of spontaneous panic attacks has been reported in patients with asthma.[4] This figure is not dissimilar to the 29% of asthmatic patients labelled by Thomas et al as having experienced dysfunctional breathing and again suggests appreciable overlap. The lifetime prevalence of asthmatics meeting DSM-III-R criteria for panic disorder in the same study was 9.7%[4].

We reported a significant excess of panic attacks and panic disorder among primary care and hospital patients with hypertension compared with matched normotensive people, and 202 of 287 people who had experienced panic attacks related "shortness of breath" or "difficulty catching breath" as symptoms in their worst panic attack.[5] The relation of history of panic attacks to a patient's sex in our sample was strikingly similar to that reported for dysfunctional breathing[1], with a significant excess in female patients of around 15% in both studies.

The importance of considering panic disorder in a discussion of dysfunctional breathing lies in the availability of treatment of proved efficacy. Thomas et al limit their consideration of therapeutic intervention to breathing therapy. In a patient with recurrent difficult breathing and history suggestive of panic disorder, a much broader range of treatment, from tricyclic antidepressants and selective serotonin reuptake inhibitors to cognitive therapy, may be effective. Failure to identify panic attacks or panic disorder may deprive patients of valuable treatment options, some of which can be instigated in primary care.

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Trial shows benefits of Buteyko breathing techniques

Editor—Keeley and Osman in their editorial say that there is no good evidence that breathing therapy benefits patients with asthma.[1] A medical trial, however, run in 1994 at the Mater Hospital, Brisbane, Australia, clearly showed that asthma patients derive great benefits from learning the Buteyko breathing techniques.[2]

For example, usage of reliever medication in the Buteyko group was reduced by an average of 90% after six weeks, and usage of steroid preventer medication was reduced by an average of 49% after three months (with no significant changes in medication usage in the control group). The 39 asthma patients who participated in this double blind trial were not selected on the basis of dysfunctional breathing but merely on the basis that they all used reliever and preventer medication. The fact that this research has not lead to dozens of follow up studies, but instead was followed by dead silence, raises many questions in my mind. One of the problems is that the Buteyko approach is "foreign" in the true sense of the word to most asthma specialists. It is a new approach to asthma, and we need a new approach as the current approach does not seem to offer anything that even slightly resembles a "cure" for the ever growing number of patients with asthma. Let's be honest: many patients end up on a lifelong regimen of drug treatment.

The second issue is that Buteyko cannot be sold over the counter of a pharmacy, which is why pharmaceutical companies are not interested—and as a consequence, it seems, neither are many medical practitioners. The third issue is that the method actually helps many patients with asthma to lead a life free of symptoms and medication. I agree, there is not much continuing profit in such an approach, but there is an enormous benefit to the patient—and was that not what medicine was all about?

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Author's reply

Editor—We reported a high prevalence of symptoms compatible with dysfunctional breathing in patients diagnosed and treated for asthma in the community and suggested that this may offer a therapeutic opportunity to improve outcomes of care in these patients. We agree with Davies et al that the prevalence of dysfunctional breathing in the general population needs to be established, although previous studies from the Netherlands have quoted a prevalence of symptomatic hyperventilation of 6-10% in general practice, much lower than the prevalence that we found in patients with asthma.[1]

We agree that there is likely to be an overlap between asthma, anxiety, panic disorder, and hyperventilation, and we believe that further studies are needed to clarify this relation. Such studies will need to measure anxiety and panic indices, and investigate physiological measures of respiration and severity of asthma. The 23% prevalence of spontaneous panic attacks quoted by Davies et al is, however, a lifetime prevalence,[2] whereas the 29% prevalence of symptoms compatible with dysfunctional breathing that we reported is a cross sectional prevalence at a single moment in time and so is likely considerably to underestimate the lifetime prevalence of such symptoms.

Davies et al raise the possibility that different types of therapeutic intervention, such as antidepressant drugs and cognitive therapy, may improve outcomes in these symptomatic patients. We agree that studies investigating the effectiveness of appropriate interventions are warranted and believe that simple and safe non-pharmacological treatments that have been shown to be effective for dysfunctional breathing in other populations are a particularly attractive option for investigation.[3]

Kuiper raises the possibility that the Buteyko breathing technique may be generally beneficial to patients with asthma. Although this method has received considerable lay publicity, it has so far had very limited scientific scrutiny. The single published study that he quotes has important methodological flaws, both in the blinding of treatment and in the outcome measure[4]; using reduction in inhaled drugs as an end point is of dubious validity because the Buteyko method strongly encourages patients not to use such treatment. We agree, however, that most therapeutic trials for asthma are currently concerned with pharmacological interventions and that there is considerable lay interest in non-pharmacological approaches. We agree with the authors of the Cochrane review of breathing therapy for asthma that controlled studies of breathing exercises for asthma are needed to clarify the effectiveness of such interventions and the characteristics of

patients who respond to them.[5] Our study raises rather than answers questions and points to a potentially important area for further research.

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Report may lead to population collection by the back door

Editor—Ferriman reported on the report by the House of Lords Select Committee on Science and Technology into human genetic databases.[1] Only after reading the report in depth does it become clear that the recommendations would lead to the establishment of a British national population collection, which would link identifiable NHS clinical information on the 58 million people in the United Kingdom for genetic research. The proposed British biomedical population collection of 500 000 volunteers being established by the Wellcome Trust, the Medical Research Council, and the NHS would be a test run for this much bigger and more ambitious project. At the same time as the report was being compiled, section 60 of the Health and Social Care Act 2001 was passed. The linking of NHS clinical data on this scale is now legally possible under section 60 because medical information from identifiable patients can be used without consent for medical research with the approval of a committee.

The adoption of the select committee's recommendations would lead to the incremental establishment of a population collection without adequate public consultation and in violation of international standards that have been set. In the United Kingdom, section 60 means that individual consent for the use of clinical data in a national population would probably not be necessary. Iceland's population collection has shown that the standards that have applied for epidemiology cannot readily be applied to genetic research on large databases of personal information. Consent, or the possibility of being able to choose if your clinical data are used for research purposes, has become the norm for population collections. Alongside this go transparency, public consultation, and debate.

Although this is an exciting project with enormous potential for the United Kingdom in terms of health care, research, and income generation, we run the risk of becoming the pariahs of the international medical research community unless the standards that have been developed for population collections are followed. The House of Lords report is only the beginning—the issues of public consultation, consent, data security, access, and oversight mechanisms of a population collection need now to be fully explored and considered. We need to make sure we do it right, so that the proposed United Kingdom national population collection is an example of exemplary practice in genetic research, rather than another Alder Hey and an embarrassment to us all.

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New global strategy on infant feeding needs to be flexible

Editor—We are concerned about the responses to a press release issued by the World Health Organization that announced the conclusions and recommendations of an expert consultation convened to examine current recommendations on feeding infants.[1] The consultation recommended exclusive breast feeding for six months, with introduction of complementary foods and continued breast feeding thereafter—a change from the previous recommendation to breast feed exclusively for four to six months.[2]

This change in the WHO's stance confirms the need for evidence based guidelines. The 1995 recommendations are still current policy,[2] and it can be gleaned from recent documentation that flexibility in recommendations is central to the WHO's strategy. Subsequently, the 54th world health assembly in May 2001 resolved to undertake serious consideration of the expert consultation's recommendations (resolution 54.2).

As authors of a systematic review on complementary feeding,[3] we were surprised that the consultation considered that current scientific evidence provided adequate data on which to recommend a change. Our review reported that, out of 33 included studies, 13 contained data supporting current recommendations and an equal number contained data supporting a recommendation for exclusive breast feeding to six months; the remainder were unable to provide evidence to support or refute the need for a change in current recommendations. We concluded that there is a lack of clear evidence to either support or refute a change to the current recommendations.

The WHO systematic review, in common with ours, acknowledged the existence of subgroups of infants for whom exclusive breast feeding for six months could not support adequate growth or nutritional status and for whom an age range for complementary feeding commencement may be more appropriate. In terms of morbidity, there is evidence, particularly in less developed settings, for a protective effect of exclusive breast feeding for six months against gastrointestinal infections. But other evidence suggests that late introduction of complementary foods—when breast milk no longer supplies the infant's energy and nutrient needs—may also have detrimental effects.

What emerges is the need for an analysis of the risks and benefits regarding complementary feeding within specific populations. Although it is essential that health professionals who advise mothers need clear and unambiguous guidance, this should allow for some flexibility toward the individual. The structure of the revised global strategy does not currently provide this. In view of these concerns we ask that any consideration of changes to current recommendations is undertaken with prudence and caution.

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Competing interests: Since the work for our review was partly funded by a grant from Nestlé UK we are aware that some people will, for that reason, cast doubt on our conclusions. However, we would like to make it clear that source of funding has never influenced the conclusions drawn in this or any of our publications.

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HIV-1 drug resistance in primary infections in the UK

Editor—The UK Collaborative Group on Monitoring the Transmission of HIV Drug Resistance reports an estimated prevalence of transmitted HIV drug resistance in 2000 of 27%.[1]

In an ongoing study of acute primary HIV infection at St Mary's Hospital, London, England, we have identified 28 seroconverters since January 2000. All patients sequenced to date (15/28) have no evidence of drug resistant mutations in either reverse transcriptase or protease before starting antiretroviral treatment. This is substantiated by the clinical response to treatment, with all subjects achieving an undetectable viral load before starting antiretroviral treatment.

The disparity in our findings is interesting, as the two cohorts are comparable. Our cohort was predominantly infected with clade B viruses (13/15). The median age was 30.5 years. All infections were transmitted sexually, except in one intravenous drug user. A possible explanation for the disparity is that seven of our patients were infected abroad, where antiretroviral treatment is less readily available. However, whereas the

collaborative group use an 18 month window of sampling to define seroconversion, we have used a more stringent definition of six months. This should allow us to detect more transmitted mutations, as in the absence of treatment these are often lost with time owing to reduced viral fitness.

In addition, we have found that caution needs to be applied when estimating the impact of codon changes in pol before starting treatment in subjects who have never been treated with combination antiretroviral drugs. In a cohort of African patients treated at St Mary's, 30% of codons in reverse transcriptase and 37% in protease were polymorphic compared with wild type clade B HIV-1, and, of these, 6% and 22%, respectively, occurred at codons associated with resistance. However, despite these changes, no single mutation had an impact on clinical outcome with combination anti-retroviral treatment.[2]

The existence of these cohorts supports the high incidence of new infections and lack awareness of safe sex. Although approaches to encourage safer sexual behaviour are urgently needed, our data suggest that the transmission of drug resistance is a secondary, although important, factor.

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Prevalence of autism in early 1970s may have been underestimated

Editor—Recently, concerns about an apparent increase in the prevalence of autism in the general population, and the pathophysiology behind this, have been prominent in the press. Before these concerns can be addressed we need to be sure that the prevalence has truly increased. A cohort study was thought suitable to provide an insight into whether the prevalence of autistic disorders has increased.

In the British cohort 1970 study (BCS70) only five children were identified as having autism (and one as having suspected autism) at the age of 5 in disability data files. This gives a prevalence of 6/13 135 (0.45/1000)—comparable with that found in previous studies.[1 2]

A focus group consisting of practising consultants (from adult and paediatric disciplines) experienced in the diagnosis of autistic disorders was convened. This group identified several diagnostic features from the available data that they thought were important in making a diagnosis of autistic spectrum disorder. The aim was to identify whether there were missing or undiagnosed cases with current commonly used diagnostic features. The features identified from the original BCS70 questionnaire included:

- At age 5
  Restless
  Solitary; does things on own
  Fearful, afraid of new situations
  Fussy or over particular
- At age 10
  Does things on own; rather solitary
  Afraid of new situations
  Fussy or over particular
  Hums or makes odd noises
  Obsessional
  Requests must be met immediately

When an analogue scale was used, only the most extreme cases—that is, the top fifth—were identified. Cases in which the child had all features present at both age 5 and age 10 were then identified.

Using the methodology above, we identified 56 cases from 14 904 children studied at age 10, giving a prevalence of 3.76/1000. This suggests that these children have an autistic spectrum disorder when contemporary diagnostic features are used.

Our finding agrees with current lifetime prevalence figures suggested by Powell et al.[3] Thus estimates of prevalence from the early 1970s may have seriously underestimated the prevalence at that time. Confirmation of this suggestion would require contemporary assessment of the individuals involved.

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Effects of legislation restricting pack sizes of paracetamol on self poisoning

It's too early to tell yet

Editor—Any measure that will reduce the incidence of paracetamol poisoning is to be welcomed. Hawton et al report the impact of legislation restricting pack sizes of paracetamol and salicylate on self poisoning,[1] but there are major limitations in interpretation—for example, the period studied after the legislation came into force is too short (one year) for its impact to be fully assessed. This is particularly relevant in the assessment of patients with acute liver disease as the numbers are small and there will be baseline variability.[2] The data from the liver unit at King's College Hospital cross the line indicating an incidence rate ratio of 1, and the data from Leeds, Newcastle, and the Royal Free Hospital have incidences close to zero.[1]

The authors give data on blood paracetamol concentrations and mean number of tablets taken per paracetamol overdose, but these did not greatly change and would be the main determinant of outcome in early paracetamol poisoning.[3] Certainly, prothrombin time would not be expected to be a good marker, not least because of the availability of adequate treatment with acetylcysteine.

Over the same period Donogue et al examined 2020 cases of deliberate paracetamol poisoning; they concluded that the incidence did not change after pack size was restricted in the Republic of Ireland.[4] In addition, our data show that the pack size legislation is not complied with, at least in London, and considerably more than the restricted number of pills can be bought in pharmacies, supermarkets, and corner shops.[2]

In conclusion, restrictions on pack size are not being adhered to universally. It is too early to make any causal conclusions on their impact on either the incidence of paracetamol poisoning in general or acute liver failure in particular.

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Authors did not look at effects on all deliberate and accidental self poisoning

Editor—Hawton et al provide some evidence of a decrease in the severity and incidence of paracetamol and salicylate poison-

ing after pack sizes of these drugs were restricted.[1] They have not, however, considered the effect on deliberate self poisoning as a whole, or on self poisoning with other drugs.

Limiting access to one type of drug may simply increase the incidence of overdose with other potentially more dangerous substances. It is important to determine if poisoning with other agents increases.[2] Although the authors allude to this in their discussion, they mention only the small but significant increase in overdoses with paracetamol compounds and paracetamol with other drugs. Using self poisoning with paracetamol and salicylates alone as a measure of the effect of this legislation on self poisoning is erroneous and potentially dangerous.

Hawton et al have not considered the effect of the legislation on accidental poisoning in children. This is a critical public health issue and needs to be evaluated alongside deliberate self poisoning to assess the impact of any change in legislation. Data from poison information centres would be useful to evaluate any changes in paediatric accidental poisoning.

With only one year of data after the change of legislation available, it is of concern that the results are not significant for the larger liver transplant units alone. Furthermore, the biochemical data do not support the decrease in severity of cases, with no change in the mean highest blood paracetamol concentration. The slight decrease in mean highest prothrombin time is a poor measure of severity: about half of patients with paracetamol poisoning without hepatotoxicity will have a raised prothrombin time,[3] so it is a poor indicator of liver poisoning.

We are concerned that the authors conclude that the legislation has been relatively successful without properly assessing its effects on all deliberate and accidental self poisoning.

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Paracetamol should be packaged with its antidote

Editor—Paracetamol overdose is the most common cause of acute hepatic failure. Hepatocytes become sensitive to paracetamol metabolites and inflammatory mediators[1] when intracellular glutathione is depleted due to metabolism of paracetamol.[2] For this reason, many clinical conditions associated with glutathione depletion—for example, chronic alcohol abuse, multiorgan system failure, chemotherapy, and certain metabolic diseases—place patients at risk of paracetamol toxicity, even at therapeutic doses of paracetamol. In addition, patients without predisposing disease are at risk because over the counter preparations often contain paracetamol and represent sources of potential overdose.

Importantly, Hawton et al report that morbidity and mortality from paracetamol overdose decreased after legislation in the United Kingdom to restrict the package sizes of the drug.[3] As the authors note, however, restricting the package size did not completely resolve the problem.

Acetylcysteine, which provides the cysteine necessary to replenish glutathione depleted by paracetamol, is used to treat paracetamol overdose.[4] Intravenous acetylcysteine is used in some areas, but oral treatment protocols are highly effective. Treatment is most effective when started soon after paracetamol is ingested,[5] but delays are still common. We therefore suggest that toxicity caused by paracetamol overdoses, whether intentional or not, is best treated by prevention—that is, by formulating or packaging paracetamol with sufficient amounts of acetylcysteine to prevent toxicity.

Acetylcysteine preserves the antipyretic and analgesic properties of paracetamol, and its coadministration should not interfere with the effectiveness of paracetamol. As it has been used for many years at high doses with minimal toxicity, giving it at the estimated doses together with paracetamol should not pose any safety issues.

The disagreeable smell and taste of some acetylcysteine formulations, particularly those used clinically in the United States, might be a problem, but the contaminants responsible for the bad smell and taste are not present in appropriately manufactured formulations. Our estimates indicate that including <200 mg acetylcysteine per 500 mg paracetamol would prevent toxicity. We therefore do not foresee any obstacles to the introduction of acetylcysteine-paracetamol products. The efficacy of such formulations for preventing morbidity and mortality should be evaluated.

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The authors have filed a disclosure and patent application for a combination treatment of acetaminophen with acetylcysteine.

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Few rich countries attain UN's aid target for poor countries

Editor—Richards is right to emphasise that aid to poor countries needs to be well managed if it is to be effective and that the rich countries need to be as generous with their aid as with their rhetoric.[1] While the total amount of aid from rich countries continues to fall sharply, however, we have to be pessimistic about the likely effects of yet another global health fund initiative.

Perhaps it is time to lay more emphasis on the performance of individual countries in giving aid. The table shows the net overseas development aid given by countries in the Organisation for Economic Cooperation and Development as a percentage of gross domestic product in 1999, ranked from meanest to most generous.[2] The meanest country, by far, was the United States. Only Denmark, Norway, the Netherlands, Sweden, and Luxemburg gave anywhere near the United Nations target of 0.7% of gross national product.

Of course, this table takes no account of how well each country manages its aid—but grossly inadequate amounts of aid will not be effective even if they are managed superbly. As doctors, we need to do all we can to persuade our governments to be more generous with overseas aid.

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Overseas development aid in 1999

Country	% of GDP	$bn
United States	0.10	9.15
Italy	0.15	1.81
Greece	0.15	0.19
Spain	0.23	1.36
United Kingdom	0.23	3.40
Australia	0.26	0.98
Portugal	0.26	0.28
Austria	0.26	0.53
Germany	0.26	5.52
New Zealand	0.26	0.13
Canada	0.28	1.70
Belgium	0.30	0.76
Ireland	0.31	0.25
Finland	0.33	0.42
Japan	0.35	15.32
Switzerland	0.35	0.97
France	0.39	5.64
Luxemburg	0.66	0.12
Sweden	0.70	1.63
Netherlands	0.79	3.13
Norway	0.91	1.37
Denmark	1.01	1.73

GDP=gross domestic product.
Source: www.oecd.org/dac/images/ODA99amo.jpg.[2]

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EU's anti-smoking stance needs to be more than frightening

EDITOR—Under European Union rules agreed in May 2001, national governments will be able to insist that, from September 2002, tobacco manufacturers devote 30% of the front of cigarette packets and 40% of their backs to messages conveying the dangers of smoking.[1]

This reflects a wider tendency for messages aimed at motivating change in behaviour to focus on arousing fear to the neglect of telling people how they can deal with the danger.[2] More than 40 years of research on communicating messages arousing fear shows that such messages are effective only when they are accompanied by equally or more powerful messages about how to reduce the health threat.[3] Not only are messages arousing fear ineffective if provided alone; they can provoke defensive responses such as denial of personal risk, thus reducing even further the chances of changes in behaviour. If smokers are highly threatened by information about health threats—for example, by statements such as "smoking kills" and graphic pictures of cancerous lungs—they also need to know that if they stop smoking these threats will be reduced or removed and that they have a chance of being able to stop.

Therefore two messages must be provided in addition to the proposed fear arousing messages to avoid such unintended harms and increase the chances of motivating smokers to stop. These need to communicate that stopping smoking is effective in reducing or avoiding the health dangers posed by smoking and that stopping smoking can be most effectively achieved by the use of pharmacological agents provided in the context of professional support. The European Union has an opportunity to move beyond the arousal of fear to include messages that are grounded in theory and evidence. Let's hope it takes it.

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So what crop would you grow if you farmed in Kenya?

EDITOR—What would you do if you were a farmer near Kaare, a semi-arid area on the on the eastern slopes of Mount Kenya?

It's a hard life being a subsistence farmer. The cost of living is high, with medical bills, school fees (only primary education is free), let alone everything else you need. On the way to Kaare I used to drive through shambas (cultivated areas) of maize, millet, sunflower, coffee, and tobacco. I saw the seasons change: the naked fields ready for the rains, the green shoots, the crops ripening, the dried maize stems standing in the fields after the harvest.

The two cash crops around Kaare are coffee and tobacco.

Coffee needs a lot of work: tending, feeding, pruning, spraying, and processing. Once, it was worth the effort. A colleague says her father put his eight children through school, and some through university, on the proceeds of coffee. You couldn't do that now—the price of coffee has fallen; lots of people thought it was a good crop so lots of people grew it so there is too much, and a lot of the money gets lost on its way to the farmer. The coffee societies are not giving their farmers money; they give them a credit note to take to the school or hospital, which might or might not be accepted in lieu of cash.

Tobacco is different. You take your crop to the factory, you get paid promptly—not a worthless piece of paper, but something you can cash, or pay into the bank and spend as you want, or even save. There are, of course, drawbacks. You need more land to earn the same amount, which means less to grow food with. You grow it, you smoke it. Your sons grow up and smoke it. You know that eventually there will be countless people with lung cancer. But if you had a family and were faced with the choice of coffee or tobacco what would you do?

I am amazed at the number of people who would never grow tobacco on principle and who continue to struggle with coffee or other small cash crops. In the rich north it is easy to have conferences, make symbolic gestures, take the companies to court; but unless those in the north help the likes of the small farmers I used to see, tobacco and all its ills are going to be around for a long time.

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Competing interests: I am a non-smoker. I have never received a penny from the tobacco industry.

Latent tuberculosis may persist for over 40 years

EDITOR—The recurrence of tuberculous disease emphasises the failure of antimycobacterial treatment based on isoniazid to eradicate latent *Mycobacterium tuberculosis* infection. We present the follow up of a patient originally reported on in 1953 as a survivor of advanced tuberculous meningitis.[1] The original case heralded the remarkable impact of isoniazid in the treatment of tuberculosis.

The genomes of *M tuberculosis* and its human host have recently been sequenced.[2] The scientific tools are now at hand to decipher the molecular mechanisms by which the organism achieves clinical latency and to devise new therapeutic strategies to eliminate these reservoirs of infection.

In 1952 the patient was a nursing student and presented with life threatening tuberculous meningitis that had failed to respond to treatment, including intrathecal streptomycin. Treatment with newly available isoniazid resulted in complete neurological recovery. A second course of four drug antituberculous chemotherapy was given for 12 months in 1986 because of spinal tuberculosis. In 2000 she presented with fevers and a sacral ulcer associated with ischial osteomyelitis. Microbiological studies of draining fluid yielded a diagnosis of tuberculosis. Antituberculous chemotherapy was given for a third time, and the ulcer healed completely.

The central paradigm in the pathogenesis of *M tuberculosis* infection is the maintenance of latency in its human reservoir. The recurrence of the infection in this patient despite two courses of antituberculous treatment over 50 years shows the clinical consequences of such latency. It emphasises the fact that current antituberculous chemotherapy targets metabolically active mycobacteria and is ineffective against latent organisms.

Recent work has identified unique enzymatic pathways, such as the glyoxylate shunt enzyme isocitrate lyase, that are critical to the survival of latent *M tuberculosis*.[3] Specific treatment targeting such pathways may provide the key to the final eradication of *M tuberculosis*.[4]

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